09/463549

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on January 12, 2007.

Doran R. Pace, Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. GJE-35
Patent No. 7,008,766

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Daniel Henry Densham
Issued	:	March 7, 2006
Patent No.	:	7,008,766
For	:	Nucleic Acid Sequence Analysis

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Amendment Under 37 CFR §1.111 dated April 29, 2005, pages 3 and 4 (original claim 5 renumbered as claim 4; original claim 7 renumbered as claim 6) reads:**
Column 10, line 1:	Page 4 of Amendment, line 1 of claim 7:
"The method according to claim 5"	--The method according to claim 5--.

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Patent Reads:	**Amendment Under 37 CFR §1.111 dated April 29, 2005, pages 3 and 5 (original claim 6 renumbered as claim 5; original claim 32 renumbered as claim 9) reads:**
Column 10, line 41:	
"The method according to claim 4"	Page 5 of Amendment, line 1 of claim 32:
	-- The method according to claim 6 --.

Patent Reads:	**Preliminary Amendment dated January 27, 2000, page 5 (original claim 33 renumbered as claim 10) reads:**
Column 10, lines 46 and 47:	
"the further blocking group is selectively removed"	Page 5 of Amendment, lines 1 and 2 of claim 33:
	-- the further blocking group can be selectively removed --.

A true and correct copy of the Preliminary Amendment dated January 27, 2000 and the Amendment Under 37 CFR §1.111 dated April 29, 2005 accompany this Certificate of Correction. Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/kmm
Attachments: Certificate of Correction (in duplicate)
copy of Preliminary Amendment dated January 27, 2000;
copy of Amendment Under 37 CFR §1.111 dated April 29, 2005.

J:\gje\35\COC.Req.doc/DNB/kmm

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,008,766

APPLICATION NO.: 09/463,549

DATED : March 7, 2006

INVENTOR : Daniel Henry Densham

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 1, "The method according to claim 5" should read -- The method according to claim 4 --.

Line 41, "The method according to claim 4" should read -- The method according to claim 5 --.

Lines 46 and 47, "the further blocking group is selectively removed" should read -- the further blocking group can be selectively removed --

MAILING ADDRESS OF SENDER:
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,008,766

APPLICATION NO.: 09/463,549

DATED : March 7, 2006

INVENTOR : Daniel Henry Densham

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 1, "The method according to claim 5" should read -- The method according to claim 4 --.

Line 41, "The method according to claim 4" should read -- The method according to claim 5 --.

Lines 46 and 47, "the further blocking group is selectively removed" should read -- the further blocking group can be selectively removed --

MAILING ADDRESS OF SENDER:
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COPY

I hereby certify that this correspondence is being deposited with United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on April 29, 2005

Doran R. Pace, Patent Attorney

AMENDMENT UNDER 37 CFR §1.111
Examining Group 1634
Patent Application
Docket No. GJE-35
Serial No. 09/463,549

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Bradley L. Sisson
Art Unit	:	1634
Applicant	:	Daniel Henry Densham
Serial No.	:	09/463,549
Filed	:	January 27, 2000
Conf. No.	:	6468
For	:	Nucleic Acid Sequence Analysis

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 CFR §1.111

Sir:

In response to the Office Action dated January 31, 2005, please amend the above-identified patent application as follows:

In the Specification

Please insert the following paragraph on page 1, beginning at line 2:

This application is the U.S. national stage application of International patent application No. PCT/GB98/02214, filed July 24, 1998.

Please substitute the following paragraph on page 1, beginning at line 6:

The ability to determine the sequence of a polynucleotide is of great scientific importance. For example, the Human Genome Project is an ambitious international effort to map and sequence the three billion ~~basis~~ bases of DNA encoded in the human genome. When complete, the resulting sequence database will be a tool of unparalleled power for biomedical research. The major obstacle to the successful completion of this project concerns the technology used in the sequencing process.

In the Claims

1 (currently amended). A method for sequencing a polynucleotide, comprising the steps of:

(i) reacting a target polynucleotide with a polymerase, wherein said polymerase is ~~enzyme~~ immobilised on a solid support, and ~~complementary~~ nucleotides, under conditions sufficient for the polymerase reaction; and

(ii) detecting the interaction between the polymerase, the target polynucleotide and ~~a~~ each specific nucleotide complementary to the target polynucleotide~~, wherein the nucleotide~~ that is incorporated into a nascent polynucleotide being synthesized as a result of the polymerase reaction, to thereby determine the sequence of the target polynucleotide, the detection being carried out by using surface plasmon resonance to measure a change in, or absorption of, radiation that occurs during the interaction.

2 (canceled).

3 (previously presented). The method according to claim 1, wherein steps (i) and (ii) are conducted with each of the complementary nucleotides in turn, until incorporation is detected, and then repeated.

4 (previously presented). The method according to claim 1, wherein step (i) is conducted with all the complementary nucleotides present.

5 (currently amended). The method according to claim 1, wherein the ~~complementary~~ nucleotides comprise a 3' blocking group which is removed after the polymerase reaction.

6 (previously presented). The method according to claim 5, wherein the blocking group is selectively removed by pulsed monochromatic light.

7 (currently amended). The method according to claim 5, wherein the ~~complementary~~ nucleotides comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group.

8 (previously presented). The method according to claim 7, wherein the further blocking group is selectively removed by pulsed monochromatic light under conditions different from those required to remove the 3' blocking group.

9 (previously presented). The method according to claim 8, wherein the further blocking group is removed by pulsing the monochromatic light for a duration different from that required to remove the 3' blocking group.

10 (currently amended). The method according to claim 1, wherein step (i) further comprises introducing a competitive inhibitor of the polymerase ~~enzyme~~.

11 (currently amended). The method according to claim 1, wherein the target polynucleotide of step (i) is bound to the polymerase ~~enzyme~~ by a β_2 dimer complex.

12 (previously presented). The method according to claim 1, wherein the polymerase is *E. coli* DNA polymerase III or T7 polymerase.

13 (previously presented). The method according to claim 1, wherein the polymerase is Taq polymerase.

14 (previously presented). The method according to claim 1, wherein the polymerase is reverse transcriptase.

15 (previously presented). The method according to claim 1, wherein step (ii) comprises detection of a change in resonance signal over time.

16 (previously presented). The method according to claim 1, wherein the radiation is electromagnetic.

17 (previously presented). The method according to claim 16, wherein the electromagnetic radiation is in the infra-red spectrum.

18-20 (canceled).

21 (previously presented). The method according to claim 1, wherein the polynucleotide is DNA.

22-29 (canceled).

30 (previously presented). The method according to claim 1, wherein steps (i) and (ii) are conducted with each of the complementary nucleotides in turn, until incorporation is detected, and then repeated.

31 (previously presented). The method according to claim 1, wherein step (i) is conducted with all the complementary nucleotides present.

32 (currently amended). The method according to claim 6, wherein the ~~complementary~~ nucleotides comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group.

33 (previously presented). The method according to claim 32, wherein the further blocking group can be selectively removed by pulsed monochromatic light under conditions different from those required to remove the 3' blocking group.

34 (previously presented). The method according to claim 33, wherein the further blocking group is removed by pulsing the monochromatic light for a duration different from that required to remove the 3' blocking group.

35 (canceled).

36 (currently amended). The method according to claim 1, wherein the ~~complementary~~ nucleotides are not labeled.

37 (previously presented). The method according to claim 1, wherein the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide.

Remarks

Claims 1, 3-17, 21, 30-34, 36, and 37 are pending in the subject application. Applicant gratefully acknowledges the Examiner's withdrawal of the rejections under 35 USC §103(a). By this Amendment, Applicant has amended the specification to correct an inadvertent typographical error and to indicate that the subject application is the U.S. national stage application of International patent application No. PCT/GB98/02214 as the first paragraph of the specification. In addition, Applicant has amended claims 1, 5, 7, 10, 11, 32, and 36. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 3-17, 21, 30-34, 36, and 37 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicant's representatives would like to thank Examiner Sisson for the courtesy of the interview conducted on April 27, 2005. Applicant respectfully submits that the amendments to the claims and specification and the remarks presented herein are in accordance with the substance of the interview conducted with the Examiner and that the subject application is in condition for allowance. For example, the claims have been amended to delete reference to "enzyme" where a polymerase is being referenced.

The application is objected to on the grounds that the subject specification fails to comply with the sequence requirements as set forth at 37 CFR 1.821 through 1.825 as set forth on the Notice to Comply attached with the Action. Applicant notes that an Amendment Under 37 CFR §1.825 (a) Through (c) was submitted when the subject application was filed directing entry of page 16 (*i.e.*, Sequence Listing) into the specification. In accordance with the Examiner-Initiated Interview Summary dated April 1, 2005, Applicant is providing with this Amendment a duplicate of the Sequence Listing in computer readable format. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1, 3-8, 30-34, 36, and 37 are rejected under 35 USC §112, first paragraph, on the grounds they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention and on the grounds that the claims are not enabled by

the subject specification. Specifically, the Examiner indicates that the subject specification does not contain a reproducible method whereby any nucleic acid could be sequenced to completion, wherein the length of the nucleic acid can be unlimited, and wherein the nucleic acid can be "present in a heterogeneous mixture of other polynucleotides, and/or where all possible nucleotides are present and nascent sequences are allowed to develop unimpeded." The Examiner also asserts, at least in regard to claim 7, that the subject specification speculates as to the ability to practice certain elements of the invention and, therefore, does not teach that the inventors were in possession of the claimed invention as of the filing date of the application. The Examiner also asserts that the specification does not enable the claimed method whereby dual blocking groups are utilized and can be selectively removed.

Applicant respectfully asserts that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention and that the claims are enabled by the subject specification. Applicant notes that claim 1 has been amended to clarify that, in practicing the claimed method, each complementary nucleotide that is incorporated during the processing of the polymerase is detected. This provides that the nucleotide sequence of the polynucleotide can be determined regardless of the speed of the reaction.

In regard to the issue of polynucleotide length, Applicant respectfully asserts that the claimed method can be used with any length polynucleotide. There is no evidence to suggest an upper limit on length of the polynucleotide that can be sequenced using the claimed method. The Examiner also indicates that the issue of length of the polynucleotide also raises the possibility of self-self duplex formation. Applicant respectfully notes that polymerases can "undo" self-self duplexes and continue processing along the polynucleotide strand.

In regard to the issue of sequencing a target polynucleotide in a heterogeneous mixture of polynucleotides, Applicant respectfully points out that the claimed method utilizes surface plasmon resonance (SPR) to measure a change or absorption of radiation that occurs during the interaction of the polymerase, the target polynucleotide, and the complementary nucleotide that is incorporated into the nascent polynucleotide during the sequencing reaction. Applicant respectfully submits that SPR is conducted at a very localized region on the solid support and, therefore, can be used in

measurements at the single molecule level. Support for this can be found in the subject specification at, for example, page 5, lines 21-33, and page 6, lines 7-14.

Also under these rejections, the Examiner asserts that the claims can be interpreted as encompassing binding of the polymerase to a target polynucleotide where the polynucleotide is bound directly or indirectly to the support. By this Amendment, Applicant has amended claim 1 to specify that the polymerase is itself immobilized on the solid support. Applicant notes, however, that the immobilization of the polymerase to the solid support can be either through direct binding to the support, or through indirect binding, such as by a linker molecule attached to the support wherein the polymerase is bound to the linker molecule. The Examiner also questions whether sequencing using the claimed method can occur where all possible nucleotides are present in the reaction mixture but wherein the nucleotides do not contain blocking groups. Applicant respectfully asserts that all nucleotides can be present and unblocked in the claimed method. In this situation, the polymerase reaction will occur at a faster rate and, therefore, detection can be achieved using appropriate readout technology.

In regard to claim 7, the Examiner indicates that the subject specification does not provide support for the method where nucleotides that are blocked at both the 3' and 5' end are utilized since it is not clear that the blocking groups can be selectively removed. Applicant respectfully asserts that the subject specification does teach that blocking groups can be used that can be selectively removed based on their spectral absorbance. See, for example, the middle of page 8 through to the middle of page 9 and page 12 of the subject specification which teach 3' and 5' blocking groups and selective removal thereof.

Applicant respectfully asserts that the claims do find written description and are enabled by the subject specification. In view of the above, reconsideration and withdrawal of the rejections under 35 USC §112, first paragraph, is respectfully requested.

Claims 1, 3-8, 30-34, 36, and 37 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1-5 of U.S. Patent No. 6,623,929. Applicant respectfully traverses and asserts that the claims are not obvious over the cited patent. Applicant respectfully asserts that the claims in the subject application are patentably distinct from the claims of the '929 patent. Claim 1 of the '929 patent is <u>not</u> directed to a method of sequencing; rather,

claim 1 of the '929 patent is directed to a method of polynucleotide synthesis. Moreover, the method of the '929 patent requires modulating the conformation of the polymerase using monochromatic light. Claim 1 of the subject application does not recite an element or limitation wherein the conformation of the polymerase is modulated by monochromatic light. In addition, the claims of the '929 patent do not teach or suggest detecting the interaction between polymerase, the target polynucleotide and the complementary nucleotide. Accordingly, Applicant respectfully asserts that the claims of the subject application are not obvious over the claims of the '929 patent. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 3-8, 30-34, 36, and 37 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1, 9, 11, 12, 16, 17, 21, and 22 of co-pending Application No. 10/478,036. Applicant respectfully traverses and asserts that the claims of the subject application are not obvious over the claims of the '036 application. Claim 1 of the subject application relies upon SPR to detect a change in or absorption of radiation that occurs during interaction of the polymerase, the target polynucleotide, and the complementary nucleotide. Claim 1 of the '036 application relies on measurement of a non-linear optical signal or a linear signal coupled to a non-linear signal. Claim 21 of the '036 application further recites that the claimed method can further comprise the application of localized SPR. In the claimed method of the '036 application, SPR may be used to enhance the signal to be detected (see, for example, page 9, lines 28-32, of the '036 application) but SPR does not replace the signal and is not used in the actual detection. Thus, the claims in the '036 application do not teach or suggest the use of SPR to detect a change in or absorption of radiation that occurs during interaction of the components used in the method. Accordingly, Applicant respectfully asserts that the claimed method of the subject application is not obvious over the claims of the '036 application. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 3-8, 30-34, 36, and 37 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1-18 of co-pending Application No. 10/786,951. In order to expedite prosecution of the subject application to completion, Applicant has submitted a Terminal Disclaimer with this Amendment which obviates this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/sl
Attachments: Terminal Disclaimer; Sequence Listing in computer readable format

COPY

January 27, 2000

PRELIMINARY AMENDMENT
Patent Application
Docket No. GJE-35

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Daniel Henry Densham

Docket No. : GJE-35

For : Nucleic Acid Sequence Analysis

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified patent application as follows:

In the Specification

After page 19: Please insert as new page 20 the attached Abstract of the Disclosure.

In the Claims

Claim 2, line 1: Delete "A" and insert --The--.

Claim 3, line 1: Delete "A" and insert --The--.

Claim 3, line 1: Delete "or claim 2".

Claim 4, line 1: Delete "A" and insert --The--.

Claim 4, line 1: Delete "or claim 2".

Claim 5, line 1: Delete "A" and insert --The--.

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JAN 23 2007

Claim 5, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 6, line 1: Delete "A" and insert --The--.

Claim 7, line 1: Delete "A" and insert --The--.

Claim 7, line 1: Delete "or claim 6".

Claim 8, line 1: Delete "A" and insert --The--.

Claim 9, line 1: Delete "A" and insert --The--.

Claim 10, line 1: Delete "A" and insert --The--.

Claim 10, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 11, line 1: Delete "A" and insert --The--.

Claim 11, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 12, line 1: Delete "A" and insert --The--.

Claim 12, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 13, line 1: Delete "A" and insert --The--.

Claim 13, line 1: Delete "any of claims 1 to 11" and insert --claim 1--.

Claim 14, line 1: Delete "A" and insert --The--.

Claim 14, line 1: Delete "any of claims 1 to 11" and insert --claim 1--.

Claim 15, line 1: Delete "A" and insert --The--.

Claim 15, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 16, line 1: Delete "A" and insert --The--.

Claim 16, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 17, line 1: Delete "A" and insert --The--.

Claim 18, line 1: Delete "A" and insert --The--.

Claim 18, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 19, line 1: Delete "A" and insert --The--.

Claim 20, line 1: Delete "A" and insert --The--.

Claim 21, line 1: Delete "A" and insert --The--.

Claim 21, line 1: Delete "any preceding claim" and insert --claim 1--.

Claim 24, line 1: Delete "A" and insert --The--.

Claim 25, line 1: Delete "A" and insert --The--.

Claim 25, line 1: Delete "or claim 24".

Claim 26, line 1: Delete "A" and insert --The--.

Claim 26, line 1: Delete "any of claims 23 to 25" and insert --claim 23--.

Claim 27, line 1: Delete "A" and insert --The--.

Claim 27, line 1: Delete "any of claims 23 to 26" and insert --claim 23--.

Claim 28, line 1: Delete "A" and insert --The--.

Claim 28, line 1: Delete "any of claims 23 to 27" and insert --claim 23--.

Please add the following new claims 30-35:

30. The method according to claim 2, wherein steps (i) and (ii) are conducted with each of the different nucleotides in turn, until incorporation is detected, and then repeated.

31. The method according to claim 2, wherein step (i) is conducted with all the nucleotides present.

32. The method according to claim 6, wherein the nucleotides comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group.

33. The method according to claim 32, wherein the further blocking group can be selectively removed by pulsed monochromatic light under conditions different from those required to remove the 3' blocking group.

34. The method according to claim 33, wherein the further blocking group is removed by pulsing the monochromatic light for a duration different from that required to remove the 3' blocking group.

35. The nucleotide according to claim 24, wherein the blocking group at the 3' position is an o-nitrobenzyloxycarbonyl group.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully submitted,

Doran R. Pace
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DRP/sl
Attachment: Abstract of the Disclosure

Abstract of the Disclosure

The present invention relates to a method for determining the sequence of a polynucleotide, the method comprising the steps of: (i) reacting a target polynucleotide with a polymerase enzyme immobilised on a solid support, and the different nucleotides, under conditions sufficient for the polymerase reaction; and (ii) detecting the incorporation of a specific nucleotide complementary to the target polynucleotide, by measuring radiation.